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Supporting Information

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Supporting Information

Spirocyclic Oxetanes: Synthesis and Properties

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General Information

All non-aqueous reactions were carried out using oven-dried (90 °C) or flame dried glassware under a positive pressure of dry nitrogen unless otherwise noted. Tetrahydrofuran, diethyl ether, toluene, and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, *Karl–Fischer* titration).[1] Dioxane was distilled from calcium hydride under an inert atmosphere.

Triethylamine was distilled from KOH under an atmosphere of dry nitrogen. All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F_{254} or Merck Aluminum oxide 60 F_{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230-400 mesh) or Machery Nagel neutral Aluminium Oxide (Brockmann activity 1, deactivated with 6 w% water) using a forced flow of eluant at 0.3-0.5 bar.[2] Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure, unless otherwise stated. Purified compounds were further dried for 12-72 h under high vacuum (0.01-0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Melting points: measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

NMR spectra: NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for 1H and 13C acquisitions, respectively Chemical shifts (d) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (d 7.26) for 1H, and chloroform (d 77.0) for 13C. All 13C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz.

IR spectra: recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm^{-1}).

Mass spectra: recorded by the MS service at ETH Zürich. EI-MS (*m*/*z*): VG-TRIBRID spectrometer. MALDI-MS (*m*/*z*): IonSpec Ultima Fourier Transform Mass Spectrometer.

Elemental analyses: performed at the Mikrolabor der ETH Zürich.

Chemical names: generated with AutoNom 2.02 (Beilstein Informationssysteme GmbH) or ChemDraw Ultra 11.0 (CambridgeSoft) and modified where appropriate.

Determination of solubility at thermodynamic equilibrium

For each compound, a sample of approximately 2 mg was added to ca 150 µL of a 50 mM aqueous phosphate buffer and transferred to a standard 96-well plate at room temperature (22.5±1°C). The pH of each compound suspension was adjusted to pH 10 by using a concentrated NaOH solution and the 96-well plate was placed on a plate shaker which agitated the suspensions over night. At the next day the samples were filtered with a micronic filter plate (MSGVN2250) to separate the solid material from the solution. After confirming unchanged pH of the solutions by way of micro-pH-meter measurements, the solution concentrations were determined by calibrated HPLC. The calibrations were obtained by HPLC analysis of different concentrations of each compound in DMSO.

Determination of lipophilicity ($\log D^{pH=7.4}$)

The high-throughput assay method is derived from the conventional 'shake flask' method:
The compound of interest is distributed between a 50mM aqueous TAPSO buffer at pH 7.4 and 1-octanol. The distribution coefficient is then calculated from the difference in concentration in the aqueous phase before and after partitioning and the volume ratio of the two phases.
To measure logD values within the range of -1 to 3.5, it is necessary to carry out the procedure at four different octanol/water ratios.
The "one-phase-analysis" experiment starts with 2 or 9 µL of a pure DMSO-solution of the compound, which is dispensed into, respectively, 38 or 171 µL of the aqueous buffer solution, bringing the compound concentration to approximately c = 0.5 mM. A small part of this solution is then analyzed by UV. The observed optical density corresponds to the concentration of the substance before partitioning.
To a measured aliquot of the aqueous solution a matching aliquot of 1-octanol is added, and the mixture is incubated by quiet shaking for 2 hours at 23±1°C. The emulsion is allowed to stand over night at the same temperature to ensure that the partition equilibrium is reached. Then, thorough centrifugation at 3000 rpm for 10 min is applied to

separate the layers, and the concentration of the compound in the aqueous phase is determined again by measuring the UV-absorption under the same conditions as the reference.

High-throughput measurement of ionization constants (pK_a)

ProfilerSGA
Ionization constants are determined at 23±1°C by spectrophotometry using a ProfilerSGA SIRIUS instrument in buffered water solution at an ionic strength of 150 mM. To this end the UV-spectrum of a compound is measured at different pH values. The solution of the sample is injected at constant flow rate into a flowing pH gradient. Changes in UV absorbance are monitored as a function of the pH gradient. The pK_a values are found and determined where the rate of change of absorbance is at a maximum.
The pH gradient is established by proportionally mixing two flowing buffer solutions. The buffer solutions contain mixtures of weak acids and bases that are UV-spectroscopically transparent above 240 nm.
It is necessary to calibrate the gradient in order to know exactly the pH at any given time. This is achieved by introducing standard compounds with known pK_a values.
In cases where the pK_a could not be measured with the ProfilerSGA system due to an insufficient UV absorption of the compound the pK_a values were measured by potentiometric titration (GLpKa). Internal validation studies (data not shown) proved that the difference between the pK_a values measured with both instruments were within the experimental error of the individual experiments.

GLpKa
pK_a values with low UV absorption were determined by potentiometric titration (SIRIUS GLpKa Analyzer) in aqueous solution, containing 0.15M KCl to adjust ionic strength. To measure pK_a of substances by the pH metric technique, a certain amount of sample was dissolved in the background electrolyte solution and acidified to pH 2 by addition of 0.5M HCl. The solution was then titrated with standardized base (0.5M KOH) to pH 12 at constant temperature (23°C) under an atmosphere of argon to minimize absorption of atmospheric CO_2. The pK_a values were then calculated by shape analysis of the titration curve in comparison to the blank titration curve.

Determination of metabolic stability in liver microsomes

Microsomal incubations were carried out in 96-well plates in 200 µL of liver microsome incubation medium containing potassium phosphate buffer (50mM, pH 7.4), $MgCl_2$ (10mM), EDTA (1mM), $NADP^+$ (2mM), glucose-6-phosphate?2H_2O (20 mM), glucose-6-phosphate dehydrogenase (4 units/ml) with 0.1mg of liver microsomal protein per mL. Test compounds were incubated at 2 µM for up to 30 min at 37°C under vortexing at 800 rpm. The reaction was stopped by transferring 30 µL incubation aliquots to 90 µL of ice-cold methanol. Levels of non-metabolized drug were determined by high-performance liquid chromatography (HPLC) coupled with tandem-mass spectrometry (LC/MS/MS). The system consisted of a Shimadzu binary gradient HPLC system, a Waters XTerra® MS C18 column (1mm * 50mm) and a Sciex API 2000 mass spectrometer. A two-component mobile phase, pumped at 0.15 mL/min, contained the following solvents: solvent A (1% aqueous formic acid and MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. The intrinsic clearance (Cl_{int}) was determined in semi-logarithmic plots of compound concentrations *versus* time.

Determination of chemical stability in aqueous solutions

The chemical stability of a given compound is determined in aqueous solutions at pH 1, 4, 6, 8, 10. Commercially available buffer systems from Merck KGaA, Darmstadt (Catalog numbers 109881, 109884, 109886, 109888, 109890) are used. An aqueous stock solution of 10 mM of each sample is prepared and diluted at a ratio of 1:20 (v/v) with buffer solution before they are shaken for 10 min at 37 °C. The solutions are then transferred to a filter plate (Millipore MSGVN2250, pore size 0.22 µm) and filtrated into V-bottom plates (from ABGene, AB-0800) that are heat-sealed prior to analysis by HPLC. Samples are taken at time points 0h and 2h and analyzed by HPLC. The percentage of recovered unchanged compound is determined by calibrated HPLC. A compound is classified as "chemically unstable" if after 2 hours less than 90% of the initial concentration is detected.

x-ray structure determination:

Data were collected on a Gemini R Ultra diffractometer (Oxford Diffraction, Abingdon, UK) by RT for Compound **3** and by 100K for compound **7** and **8** using Cu-K-alpha-radiation (1.54184Å) and processed with the Crysalis-package. Structure solution and refinement was performed using the ShelX software[3] (Sheldrick 2008).

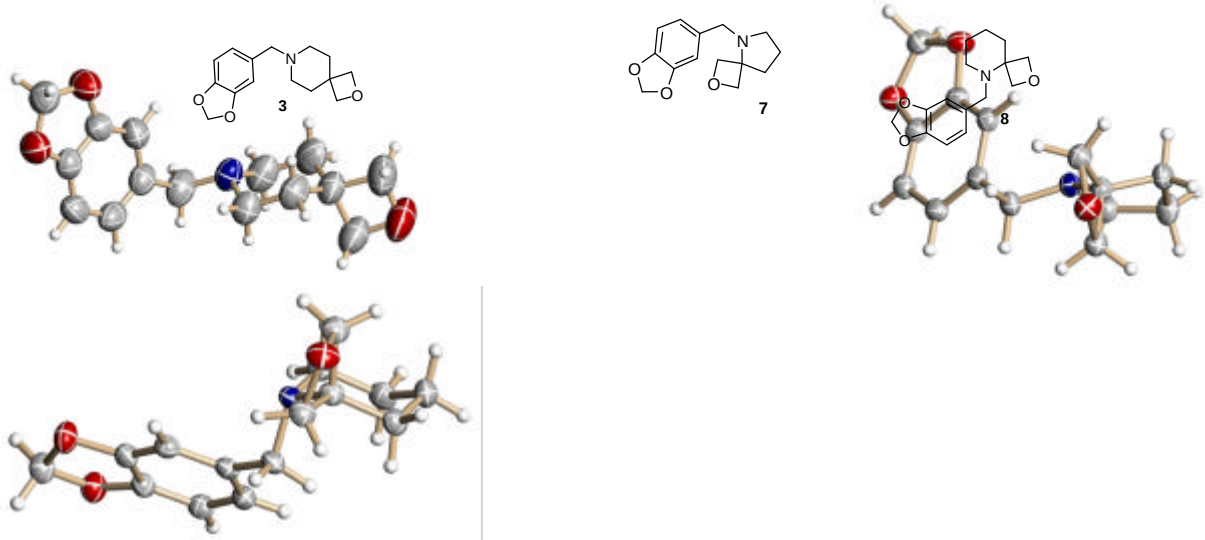
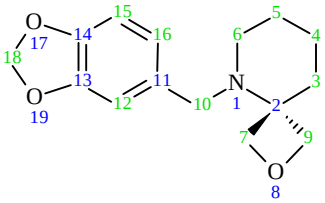


*Figure: x-ray structures of spirocycles **3**, **7** and **8** illustrating the influence of the oxetane on ring geometry.*

NMR spectroscopic analysis of N-piperonyl-piperidine 11

1) Free base 11

The free base is not sufficiently soluble in water for good NMR-spectroscopic analysis. ^{1}H-NMR spectra in DMSO-d_6 and $CDCl_3$ show nearly the same chemical shifts and couplings. The signals for the methylene piperidine protons show typical averaged signal multiplets of protons due to fast ring/nitrogen inversion of the piperidine ring:



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (m, 2 H, H-4) 1.48 (m, 2 H, H-5) 1.81 (t, *J*=6.2 Hz, 2 H, H-3) 2.30 (t, *J*=5.5 Hz, 2 H, H-6) 3.65 (s, 2 H, H-10) 4.23 (d, *J*=6.3 Hz, 2 H, H-7''/9'') 4.59 (d, *J*=6.3 Hz, 2 H, H-7'/9') 5.98 (s, 2 H- H-18) 6.80 (dd, *J*=7.9, 1.5 Hz, 1 H, H-16) 6.84 (d, *J*=7.9 Hz, 1 H, H-18) 6.90 (d, *J*=1.5 Hz, 1 H, H-12)

2) DCl salt of 11

The DCl salt form of **11** was produced by dissolving **11** in a mixture of D_2O and DCl (0.4 ml D_2O and 0.1 ml 1N DCl; pH = 1). Assignment of the signals was achieved on the basis of 2D ^{1}H,^{1}H-COSY and 2D ^{1}H,^{13}C-HSQC experiments.

By contrast to the free base, the ^{1}H-NMR spectrum of the deuterated salt shows signals for diastereotopic methylene protons at 25 °C. Even the methylene protons of the piperonyl O-CH_2-O group (C-18) at 6.04 ppm are split into a

weak AB system. The benzylic protons (CH_2-10) at 4.39 ppm give rise to a pronounced AB system. The diastereotopic nature of these methylene protons arise from the chiral quaternary nitrogen center of the deuterated piperidine. All signals of the piperidine ring methylene groups are diasterotopic and show the typical coupling constants of a chair conformation of a six-membered ring. The signals of the axial protons at C-3, C-5 and C-6 were identified unambiguously on the basis of their multiplets (large diaxial H,H couplings and/or multiplet width).

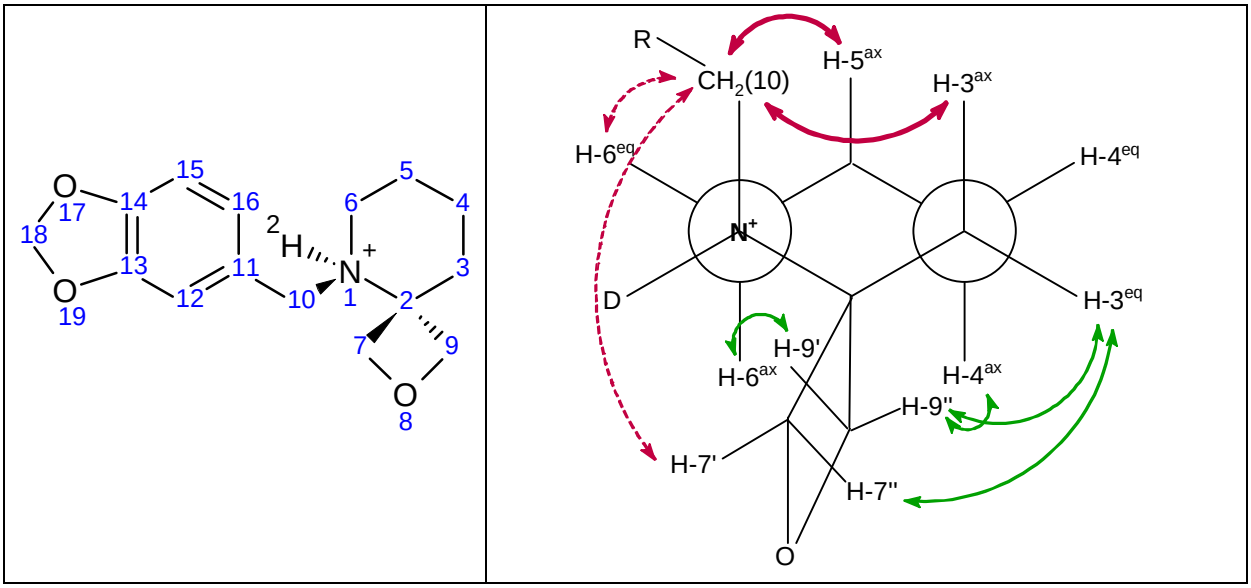


Figure 1: Chemical structure of deuterated **11** and stereochemical assignments of protons based on observed NOE's (green: NOE's identifying the oxetane protons; red: NOE's determining the axial orientation of the piperonyl group; red dotted: observed NOE's that do not allow a distinction between equatorial or axial position of the piperonyl group).

^{1}H NMR (400 MHz, D_2O/DCl*; d_4-TSP = 0 ppm*) δ ppm 1.62 (m, 1 H, H-4ax) 1.68 (m, 1 H, H-5eq) 1.84 (m, 1 H, H-4eq) 2.00 (m, 1 H, H-5ax) 2.29 (dt, *J*=15.0, 4.3 Hz, 1 H, H-3eq) 2.36 (td, *J*=15.0, 1.3 Hz, 1 H, H-3ax) 3.09 (ddd, *J*=13.7, 11.6, 3.5 Hz, 1 H, H-6ax) 3.14 (dt, *J*=13.7, 3.5 Hz, 1 H, H-6eq) 4.39 (AB, 2 H, H-10) 4.54 (d, *J*=8.3 Hz, 1 H, H-7'') 4.72 (d, *J*=8.1 Hz, 1 H, H-9'') 4.88 (d, *J*=8.3 Hz, 1 H, H-7') 5.01 (d, *J*=8.1 Hz, 1 H, H-9') 6.04 (AB, 2 H, H-18) 6.97 (m, 1 H, H15) 7.05 (m, 2 H, H-12, H-16)

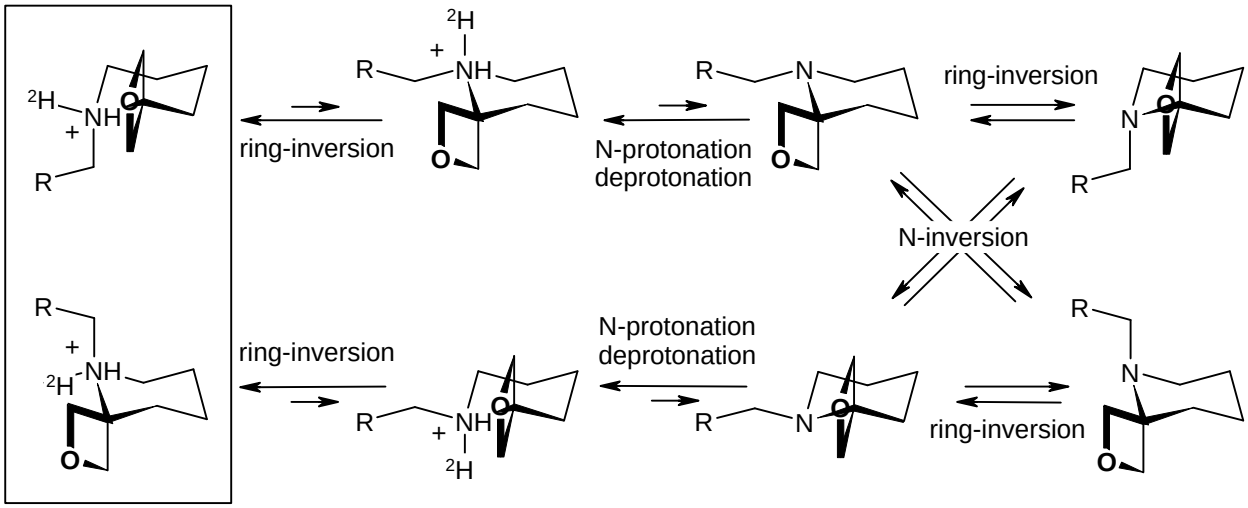
Assignments of the oxetane protons:
Based on HSQC experiments, the signals at 5.01, 4.88, 4.72, and 4.54 ppm can be assigned to the diastereotopic methylene protons of the oxetane moiety. The signal at 4.72 is assigned to one of the axial methylene oxetane protons, H-9", based on the strong NOE to H-4ax and a significant NOE to H-3eq. A strong NOE between H-6ax and the signal at 5.01 ppm defines H-9'. The proton H-7'' (4.54 ppm) is determined by a significant NOE to H-3eq.

Assignments of the spatial orientation of the piperonyl group:
The 2D-NOESY spectrum shows 4 cross peaks (cf. red arrows) for the benzylic protons (C-10). The two cross peaks between CH_2-10 and H-7' and H-6eq are ambiguous (red dotted arrows) with respect to the stereochemistry. Both, axial or equatorial orientations of the piperonyl group are compatible with the occurrence of these NOE's. The two other cross peaks are dipolar couplings between CH_2-10 and H-3ax and H-5ax respectively. These two NOE's (cf. red solid arrows) determine unambiguously the axial orientation of the piperonyl group at the piperidine ring.

The observation of only one set of ^{1}H-signals in the NMR-spectrum of deuterated **11** with well separated and sharp signals for the equatorial and axial protons is clear evidence for the predominance of the chair conformation with an axial N-piperonyl substituent (Figure 1). Furthermore, the clear differentiation into axial and equatorial piperidine ring protons as well as the absence of NOE's between the benzylic protons and H-6ax excludes a rapid equilibrium

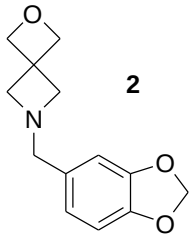
at 25 ºC between enantiomeric N-deuterated chair forms with the N-piperonyl group axial *via* a sequence of rapid de-deuteration, ring- and N-inversion, and re-deuteration processes (Scheme 1).

Scheme



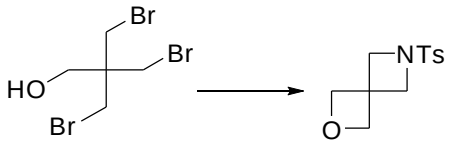
Experimental Procedures:

Oxetanes



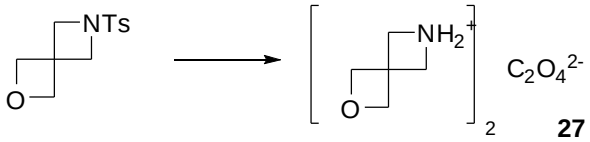
2

6-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-6-azaspiro[3.3]heptane ***2***



To a solution of KOH (33.23 g, 0.5923 mol, 3.200 equiv) and *p*-tosylamide (37.96 g, 0.2217 mol, 1.200 equiv) in 600 ml ethanol 3-Bromo-2,2-bis(bromomethyl)propan-1-ol (60.12 g, 0.1851 mol, 1.000 equiv) was added at room temperature and the reaction mixture was heated to reflux for 90 h. The solvent was removed by evaporation, 500 ml 1 M KOH was added and the white suspension was left to stir for another 2 h at room temperature. The mixture was filtered and the white filter cake was rinsed with water until the washing water was neutral. The filter cake was dried under high vacuum to give 30.55 g of product containing 10 mole-% of tosylamide as a white solid. The overall yield of pure N-tosyl-2-oxa-6-azaspiro[3.3]heptane was calculated to be 27.38 g (58 %).

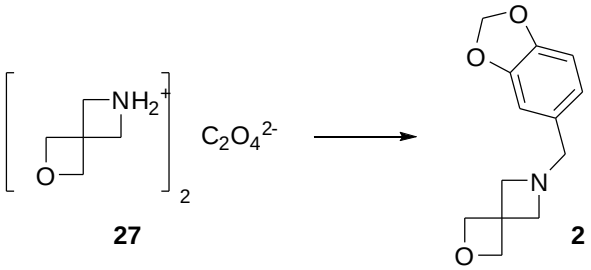
R_f = 0.14 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H, J=8.3Hz), 7.37 (d, 2H, J=8.0Hz), 4.59 (s, 4H), 3.91 (s, 4H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 131.6, 130.0, 128.5, 80.5, 59.7, 37.7, 21.8; IR (thin film) ν 2930, 2865, 1958, 1846, 1687, 1595, 1459, 1442, 1335, 1312, 1292, 1209, 1165, 1143, 1039, 973, 943, 890, 829, 683, 542 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_3S$; C, 56.90; H, 5.97; N, 5.53. Found: C, 56.79; H, 5.98; N, 5.48. HRMS (EI) calcd for $C_{12}H_{15}NO_3S$: $[M]^+$ = 253.0768, Found: 253.0769.



27

N-tosyl-2-oxa-6-azaspiro[3.3]heptan (7.30 g, 28.8 mol, 1.00 equiv) and magnesium granulate (4.90 g, 0.202 mol, 7.00 equiv) were sonicated for one hour in methanol (500ml). Almost all solvent was removed from the grey reaction mixture on a rotary evaporator to give a viscous grey residue. Diethyl ether (500 ml) and sodium sulfate decahydrate (15g) were added and the resulting light grey mixture was stirred vigorously for 30 minutes before filtration. The filtrate was dried over anhydrous sodium sulfate and anhydrous oxalic acid (1.30 g, 14.4 mol, 0.500 equiv) dissolved in Ethanol (~1 mL) was added to the organic phase. A thick white precipitate formed instantly. It was filtered off and dried under vacuum to give 3.37 g (81.0 %) of amorphous white solid. The obtained product showed the anticipated signals in 13C-NMR and 1H-NMR with no impurities but did not pass elemental analysis. This may be due to the presence of a certain fraction of the hydrooxalate salt in the product.

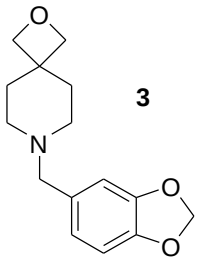
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (s, 4H), 4.34 (s, 4H), 2.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 79.9, 54.5, 40.0; IR (thin film of 2-Oxa-6-aza-spiro[3.3]heptane) ν 3400, 2953, 2875, 1653, 1556, 1431, 1352, 1315, 1250, 963, 829, 774 cm^{-1}; HRMS (EI) done with 2-Oxa-6-aza-spiro[3.3]heptane, calcd for C_5H_9NO $[M-H]^+$ = 98.0601, found 98.0603.



27 **2**

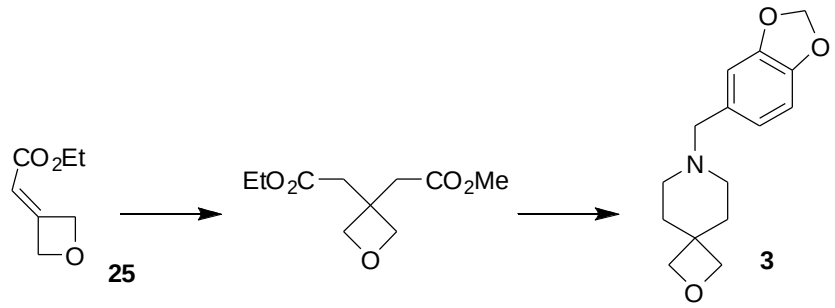
Piperonal (1.0 g, 6.9 mmol, 1.3 equiv) was dissolved in 20 ml methylene chloride and to the solution was added 2-oxa-6-azaspiro[3.3]heptan (0.53 g, 5.3 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (2.8 g, 13 mmol, 2.5 equiv). The resulting white suspension was stirred overnight at room temperature. Saturated aqueous K_2CO_3 was added until complete dissolution of the borate byproducts. The aqueous phase was extracted with EtOAc 3 times. The combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in 250 ml diethyl ether and a solution of anhydrous oxalic acid (0.4805 g, 5.3 mmol, 1 equiv) in little ethanol was added. The white precipitation formed was filtered, washed with diethyl ether and then dissolved in 1 M KOH. The aqueous phase was extracted with EtOAc, the combined organic phases were dried over Na_2SO_4, filtered evaporated to give 0.91 g (74 %) of clear white liquid as pure product.

R_f = 0.24 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, 2H, J=7.3Hz), 7.48 (d, 2H, J=8.5Hz), 7.40 (t, 2H, J=7.6Hz), 7.30 (m, 1H), 6.53 (d, 2H, J=8.5Hz), 4.86 (s, 4H), 4.07 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.5, 131.5, 121.4, 108.8, 107.9, 100.8, 81.3, 63.4, 63.1, 38.9; IR (thin film) ν 2931, 2863, 2815, 1608, 1503, 1410, 1442, 1377, 1247, 1110, 1039, 973, 927, 869, 811, 774, 746 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C: 70.92, H: 6.45, N: 6.89, O: 15.74, found C: 70.80, H: 6.53, N: 6.88, O: 15.79; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$ 233.1047, found 233.1052.



3

7-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-7-azaspiro[3.5]nonane 3

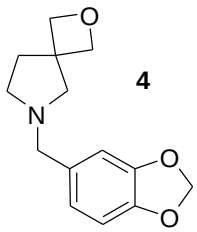


25 **3**

To a solution of dimethyl malonate (1.1 mL, 9.6 mmol, 3.2 equiv) in 25 mL dry THF was added Sodium hydride (60 w% suspension in mineral oil, 0.32 g, 8.0 mmol, 2.5 equiv) at rt. After stirring for 20 minutes, tetrabutyl ammonium bromide (0.32 g, 1.0 mmol, 0.30 equiv) was added, followed by a solution of the a,ß-unsaturated ester **25** (0.43 g, 3.0 mmol, 1.0 equiv) in 1 mL dry diethyl ether. The mixture was stirred overnight at room temperature and quenched by adding 0.47 mL glacial acetic acid. The solvent was evaporated and the residue treated with diethyl ether. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The residue was dissolved in 30 mL DMSO, water (150 µL) and sodium chloride was added and the mixture stirred at 160 °C for 2 h. Brine and diethyl ether (200 mL) were added and the organic phase washed twice with brine. The organic phase was dried over $MgSO_4$, filtered, evaporated and the residue being product (R_f = 0.31 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (m, 4H), 4.12 (q, 2H, J = 7.1 Hz), 3.67 (s, 3H), 2.93 (s, 2H), 2.90 (s, 2H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.8, 81.0, 60.5, 51.6, 40.0, 39.8, 38.8, 14.2; IR (thin film) ν 2934, 1736, 1440, 1375, 1176, 1070, 1028, 978 cm^{-1}) of good purity used without further purification. This crude material was dissolved in 30 mL dry diethyl ether, the solution cooled to 0 °C and $LiAlH_4$ (3 mL, 4.0 M in diethyl ether, 12 mmol, 3.8 equiv) added dropwise leading to white precipitation. After stirring for 3 h at 0 °C, Na_2SO_4?10H_2O was cautiously added. The mixture was filtered after stirring for 20 minutes. The filter cake was boiled with two portions of 20 mL EtOAc. The combined filtrates were dried over Na_2SO_4, filtered, evaporated and the residual diol (^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (s, 4H), 3.78 (t, 4H, J = 6.4 Hz), 2.06 (t, 4H, J = 6.4 Hz), 1.94 (s, 2H)) dissolved in 30 mL dry methylene choride. The solution was cooled to 0 °C, MsCl (0.74 mL, 9.6 mmol, 3.0 equiv) was added, followed by dropwise addition of triethyl amine (1.8 mL, 13 mmol, 4.0 equiv). After stirring for 1 h, a sample in the NMR indicated full conversion. Aqueous saturated NH_4Cl was added and the aqueous phase extracted 3 times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residual bismesylate (^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (s, 4H), 4.35 (t, 4H, J = 6.4 Hz), 3.14 (s, 3H), 3.03 (s, 6H), 2.26 (t, 4H, J = 6.4 Hz)) dissolved in 4.0 mL piperonyl amine (32 mmol, 10 equiv). After stirring for 40 min at 90 °C, a sample in the NMR showed full conversion of starting material. Saturated aqueous Sodium bicarbonate was added and the aqueous phase extracted 3 times with EtOAc. The combined organic phases were washed once with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified on column (Al_2O_3, cyclohexane to 8/1 cyclohexane/EtOAc) to give 0.26 g pure product as a white solid (mp = 78 – 80 °C).

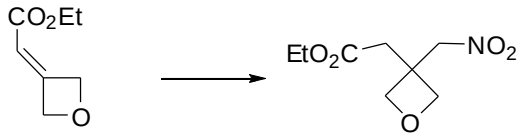
R_f = 0.54 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, 1H, J = 0.9 Hz), 6.72 (m, 2H), 5.93 (s, 2H), 4.39 (s, 4H), 3.34 (s, 2H), 2.28 (s, 4H), 1.85 (t, 4H, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4,

146.3, 132.1, 121.9, 109.2, 107.7, 100.7, 81.8, 62.9, 50.3, 38.6, 35.0; IR (thin film) ν 2924, 2858, 2361, 1480, 1441, 1370, 1241, 1099, 1039, 977, 929, 810, 688 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.00; H, 7.47; N, 5.27.; HRMS (EI) calcd for $C_{15}H_{19}NO_3$ $[M]^+$= 261.1360, found: 261.1361.



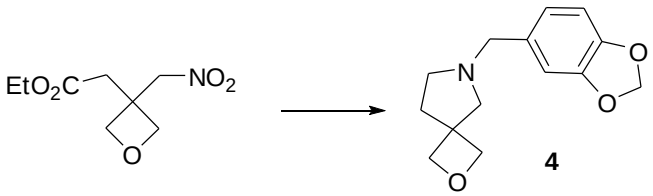
4

6-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-6-azaspiro[3.4]octane ***4***



To a solution of a,ß-unsaturated ester **25** (1.62 g, 11.4 mmol, 1.00 equiv) in 10 mL dry MeCN was added nitro methane (3.08 mL, 56.9 mmol, 5.00 equiv), followed by a catalytic amount of DBU (340 µL, 2.28 mmol, 0.200 equiv) at 0°C. After stirring for 4h at rt, the mixture was filtered through a plug of SiO_2 with 4/1 cyclohexane/EtOAc to give 2.13 g almost (>98 w% by NMR) pure material as a colorless liquid (92 % yield).

R_f = 0.26 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 2H), 4.63 (d, 2H, J=7.0Hz), 4.56 (d, 2H, J=7.0Hz), 4.16 (q, 2H, J=7.1Hz), 2.95 (s, 2H), 1.27 (t, 1H, J=7.1Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 78.6, 78.6, 61.2, 40.3, 38.1, 14.3; IR (thin film) ν 2918, 2872, 1723, 1549, 1378, 1188, 1075, 1024 977 cm^{-1}; Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45. Found: C, 47.11; H, 6.39; HRMS (EI) calcd for $C_8H_{13}NO_5$: $[M]^+$= 203.0794, Found: 203.0747.

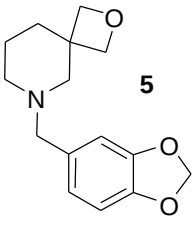


4

To a solution of (3-Nitromethyl-oxetan-3-yl)-acetic acid ethyl ester (0.64 in 15 mL dry toluene was added DibalH (1.4 M in toluene, 4.3 mL, 6.3 mmol, 2.0 equiv) at -78 °C over 15 minutes. After 30 minutes, TLC indicated full conversion. After further 10 minutes, 5 mL 1 M aqueous HCl were added and the mixture allowed to warm to room temperature. diethyl ether and another 15 mL of 1 M HCl were added and the aqueous phase extracted 3 times with EtOAc. The combined organic phases were washed once with 1 M HCl, brine and saturated aqueous sodium bicarbonate, dried over Na_2SO_4, filtered, evaporated and the residue (0.41 g) found to be ~90% pure by NMR with the residual material being the primary alcohol resulting from overreduction. (R_f = 0.15 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 4.92 (s, 2H), 4.63 (d, 2H, J=7.1Hz), 4.50 (d, 2H, J=7.1Hz), 3.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 78.8, 78.6, 47.3, 39.5; IR (thin film) ν 2934, 2819, 2734, 1715, 1545, 1428, 1382, 1258, 1097, 990, 901 cm^{-1}; HRMS (EI) calcd for $C_6H_9NO_4$ $[M\text{-}CH_2NO_2]^+$ = 99.0442; Found: 99.0446.) This material was used without further purification, dissolved in 25 mL MeOH and 48 mg $Pd(OH)_2$/C (20 w%), were added. After exchanging the atmosphere with hydrogen, hydrogen was bubbled through the mixture for 45 minutes and stirred under hydrogen overnight (balloon), when a sample in the NMR indicated clean conversion to product. The mixture was filtered through celite, evaporated and the residue (^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, 2H, J=5.9Hz), 4.60 (d, 2H, J=5.9Hz), 3.15 (s, 2H), 2.91 (t, 2H, J=7.0Hz), 2.05 (t, 2H, J=7.1Hz)) dissolved in 30 mL methylene chloride. Piperonal (0.41 g, 2.7 mmol, 1.2 equiv), followed by $NaHB(OAc)_3$ (1.2 g, 5.7 mmol, 2.5 equiv). The mixture was stirred for 7 h. Aqueous saturated K_2CO_3 (80 mL) was added and the mixture stirred vigorously for 15 minutes. The aqueous phase was extracted 3 times with methylene choride. The combined organic phases werde dried over Na_2SO_4, filtered, evaporated and the residue purified by

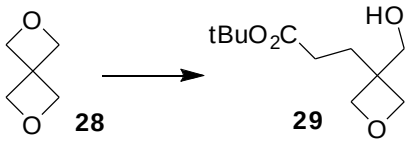
chromatography (SiO_2, 1/2 cyclohexane/EtOAc to 5 % MeOH in EtOAc) to give 0.29 g pure product as a slightly yellowish oil (53 %).

R_f = 0.2 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, 1H, J = 0.5 Hz), 6.73 (m, 2H), 5.94 (s, 2H), 4.60 (q, 4H, J = 5.9 Hz), 3.48 (s, 2H), 2.78 (s, 2H), 2.51 (t, 2H, J = 7.0 Hz), 2.11 (t, 2H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.4, 145.9, 132.6, 121.6, 109.0, 107.8, 100.7, 83.8, 64.6, 59.8, 53.4, 44.9, 36.3; IR (thin film) ν 2921, 2861, 2788, 1489, 1442, 1382, 1345, 1240, 1097, 1039, 976, 928, 809 cm^{-1}; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.71; H, 7.06; N, 5.72; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M]^+$=247.1203, found: 247.1201.



5

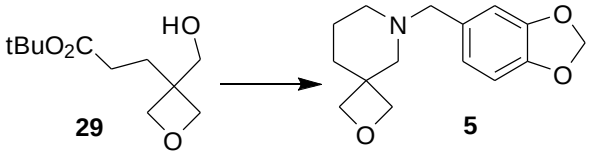
6-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-6-azaspiro[3.5]nonane ***5***



28 **29**

To a solution of *N,N*-diisopropylamine (0.48 mL, 3.6 mmol, 6.0 equiv) in 3 mL dry THF was added *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol, 5.5 equiv) at -78 °C. After stirring for 20 minutes, 3 mL dry hexane was added and stirring was continued for another 20 minutes, before *tert*-butyl acetate (0.40 mL, 3.0 mmol, 5.0 equiv) was added as a solution in dry THF (2 mL). After stirring for 25 minutes, the mixture was cooled to -95 °C (diethyl ether/liquid nitrogen) and 2,6-dioxaspiro[3.3]heptane (**28**) (60 mg, 0.60 mmol, 1.00 equiv)[4] was added, followed by dropwise addition of BF_3?OEt_2 (0.37 mL, 3.0 mmol, 5.0 equiv). The mixture was allowed to warm to -78 °C. After stirring for 2.5 h, another 0.3 mL BF_3?OEt_2 (2.4 mmol, 4.1 equiv) were added. After stirring for further 5 h, the mixture was quenched by adding saturated aqueous NH_4Cl. The aqueous phase was extracted 4 times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 2/1 cyclohexane/EtOAc to EtOAc) to give 109 mg (89 w% by NMR, rest EtOAc) product as a colorless liquid (75 % yield).

R_f = 0.31(SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, 4H, J = 6.1 Hz), 3.74 (d, 2H, J = 5.4 Hz), 2.66 (s, 1H), 2.24 (dd, 2H, J = 6.8Hz, 7.4 Hz), 2.04 (t, 3H, J = 7.0 Hz), 1.44 (d, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 81.1, 78.6, 65.4, 43.8, 30.3, 28.1, 27.9; IR (thin film) ν 3424, 2977, 2873, 1728, 1452, 1368, 1306, 1256, 1157, 1047, 977, 844 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{20}O_4$: $[M\text{-}C_4H_8]^+$= 159.0652, found: 159.0652.

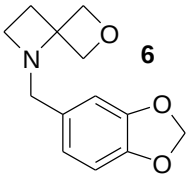


29 **5**

To a solution of 3-(3-Hydroxymethyl-oxetan-3-yl)-propionic acid tert-butyl ester (**29**) (0.16 g, 0.76 mmol, 1.0 equiv) in 25 mL dry diethyl ether was slowly added $LiAlH_4$ (4.0 M in diethyl ether, 0.57 mL, 2.3 mmol, 3.0 equiv) at 0 °C. After stirring for 45 minutes, Na_2SO_4?$10H_2O$ was added and the mixture stirred for 15 minutes. After filtration, the filter cake was boiled with two portions of 20 mL EtOAc. The combined filtrates were dried over Na_2SO_4, filtered, evaporated and the residual diol dissolved in 20 mL dry methylene choride, cooled to 0 °C and MsCl (0.18 mL, 2.3 mmol, 3.0 equiv) was added, followed by slow addition of triethyl amine (0.42 mL, 3.0 mmol, 4.0 equiv). After 1 h, a sample in the NMR indicated full conversion. Saturated aqueous NH_4Cl was added, the aqueous phase extracted 3 times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and the residue (R_f = 0.19 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (d, 4H, J = 1.2 Hz), 4.42 (d, 2H, J = 1.4 Hz), 4.28 (t, 2H, J = 6.0 Hz), 3.08 (d, 3H, J = 0.8 Hz), 3.04 (d, 3H, J = 1.0 Hz), 1.92 (m, 2H), 1.81 (s, 2H)) mixed with piperonyl amine (0.95 mL, 7.6 mmol, 10 equiv). The mixture was heated to 90 °C for 1 h, when a sample in the NMR showed full conversion. EtOAc was added and 1M aqueous KOH. The aqueous phase was extracted 3 times with EtOAc, the combined organic phases washed once with brine, dried over $MgSO_4$, filtered, evaporated and purified by chromatography (Al_2O_3, 20/1 to 8/1 cyclohexane/EtOAc) to give a mixture of product and piperonal. This material was dissolved in 40 mL diethyl ether, a solution of oxalic acid (0.76 mmol, 1.00 equiv)

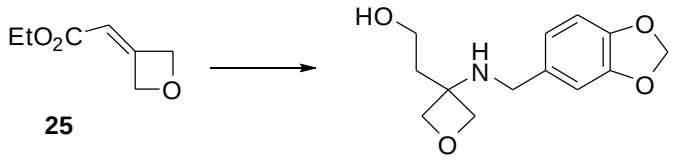
in EtOH added. The white precipitate was collected and dissolved in 1 M aqueous KOH. The mixture was extracted 3 times with diethyl ether, the combined organic phases were dried over $MgSO_4$, filtered and evaporated to give 97 mg pure product (49 %) as slightly yellowish oil.

R_f = 0.19 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.73 (m, 2H), 5.95 (s, 2H), 4.35 (q, 4H, J = 5.9 Hz), 3.40 (s, 2H), 2.51 (s, 2H), 2.30 (s, 2H), 1.68 (s, 2H), 1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.3, 132.4, 121.7, 109.0, 107.7, 100.7, 81.0, 62.8, 61.1, 53.3, 39.7, 33.5, 22.6; IR (thin film) ν 2931, 2860, 2765, 1857, 1732, 1607, 1489, 1441, 1369, 1243, 1100, 1040, 976, 931, 810 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.69; H, 7.40; N, 5.29.; HRMS (EI) calcd for $C_{15}H_{19}NO_3$: $[M]^+$= 261.1360, found: 261.1362.



6

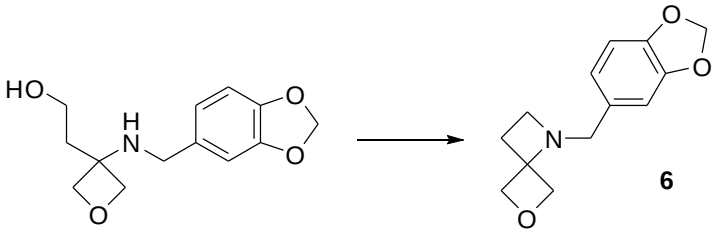
1-(benzo[d][1,3]dioxol-5-ylmethyl)-6-oxa-1-azaspiro[3.3]heptanes ***6***



25

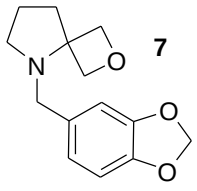
To 2-(oxetan-3-ylidene)acetate (305 mg, 2.15 mmol; 1.00 equiv) was added piperonyl amine (0.28 ml; 2.4 mmol; 1.1 Eq). This mixture was heated at 60 °C under Argon Atmosphere for 2 hours, before 30 ml dry diethyl ether were added and the reaction mixture was cooled to 0°C, $LiAlH_4$ (4.0 M in diethyl ether; 2.4 mL, 9.4 mmol, 4.0 equiv) was drop wise added, and the white suspension stirred for 2 h. Na_2SO_4?$10H_2O$ was added slowly and the mixture stirred at room temperature for 25 minutes, before it was filtered. The filter cake was cooked with 4 portions of EtOAc and the combined filtrates dried over Na_2SO_4, filtered, evaporated and the residue purified by chromatography (SiO_2; $CHCl_3$ to $CHCl_3$/MeOH 92:8) to give 399 mg (95 w% by NMR) product (70 %) as a yellowish oil.

R_f = 0.78 (SiO_2, $CHCl_3$/MeOH 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (m, 3H, J = 5.7 Hz), 5.94 (s, 2H), 4.56 (d, 2H, J = 6.7 Hz), 4.50 (d, 2H, J = 6.8 Hz), 3.82 (t, 2H), 3.72 (s, 2H), 2.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.5, 132.7, 121.5, 108.7, 108.3, 101.0, 81.4, 61.0, 59.5, 47.0, 35.1; IR (thin film) ν 3386, 2873, 1503, 1490, 1443, 1250, 1099, 1039, 975, 928.0, 810 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}NO_4$ $[M\text{-}CH_2O]^+$ = 221.1052, found: 221.1052

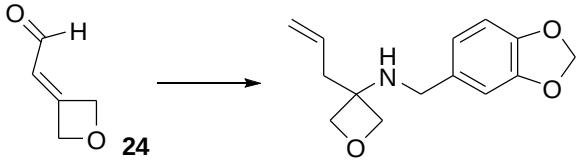


Tetrabromocarbon (750 mg, 2.26 mmol, 1.50 equiv) is added to a solution of 2-(3-(benzo[d][1,3]dioxol-5-ylmethylamino)oxetan-3-yl)ethanol (379 mg, 1.51 mmol, 1.00 equiv) and triphenyl phosphine (593 mg, 2.26 mmol, 1.50 equiv) in 25 mL dry acetonitrile (immediate orange color), followed by distilled triethyl amine (475 µL, 3.41 mmol, 2.00 eq). The flask is wrapped in aluminum foil and stirred for 40 h at rt. Brine and diethyl ether is added and the aqueous phase extracted 3 times with diethyl ether. The combined organic phases are dried over Na_2SO_4, filtered, evaporated and the residue purified by chromatography (Al_2O_3, cyclohexane to 8/1 cyclohexane/EtOAc) to give 253 mg (72%) pure product as a yellow oil that solidified upon storage in the fridge (mp = 62.5 °C, measured by DSC).

R_f = 0.15 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ; 6.85 (s, 1H), 6.76 (m, 2H), 5.93 (s, 2H), 4.97 (d, 2H, J = 7.9 Hz), 4.63 (d, 2H, J = 7.9 Hz), 3.72 (s, 2H), 3.03 (t, 2H, J = 6.8 Hz), 2.36 (t, 2H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 146.5, 131.7, 121.4, 109.0, 108.1, 100.9, 81.4, 69.1, 56.2, 49.8, 29.5; IR (thin film) ν 3403, 2939, 2864, 1608, 1502, 1490, 1442, 1377, 1347, 1247, 1185, 1117, 1094, 1038, 973, 927, 866, 810, 776 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00; O, 20.58; Found: C, 66.65; H, 6.53; N, 6.04; O, 20.78; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$ 233.1052, found: 233.1048.

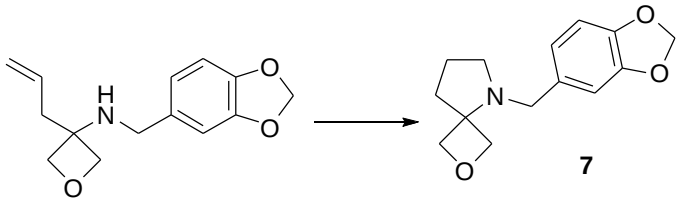


5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.4]octane ***7***



To a solution of piperonyl amine (0.82 mL, 6.6 mmol, 1.1 equiv) and DBU (9.0 µL, 60 µmol, 1.0 mol%) in 6 mL dry THF was added the a,ß-unsaturated aldehyde **24** (0.60 g, 6.0 mmol, 1.0 equiv) at -18 °C (MeOH/ice bath). After stirring for 4 h at this temperature, the solution was transferred to a solution $H_2C{=}PPh_3$ in THF (prepared by addition of *n*-BuLi (2.5 M in hexanes, 6.7 mL, 17 mmol, 2.8 equiv) to a suspension of Ph_3PMeBr (6.4 g, 18 mmol, 3.0 equiv) in 50 mL dry THF at 0 °C). The mixture was allowed to warm to room temperature and stirred over night, before water and brine were added. The aqueous phase was extracted 3 times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, evaporated and the residue purified by chromatography (Al_2O_3, 8/1 to 2/ cyclohexane/EtOAc) to give 435 mg pure product as a yellowish oil (29 %).

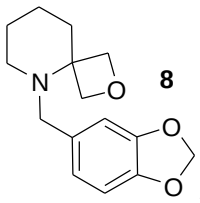
R_f = 0.68 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 1H), 6.76 (m, 2H), 5.94 (d, 2H, J = 3.7 Hz), 5.85 (m, 1H), 5.20 (m, 2H), 4.57 (d, 2H, J = 6.6 Hz), 4.43 (d, 2H, J = 6.7 Hz), 3.71 (s, 2H), 2.65 (d, 2H, J = 7.1 Hz), 1.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.5, 134.0, 132.6, 120.9, 118.6, 108.5, 108.0, 100.8, 80.7, 59.3, 46.9, 40.3; IR (thin film) ν 3312, 3072, 2398, 2870, 1640, 1607, 1503, 1490, 1442, 1250, 1099, 1037, 980, 926, 811 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M\text{-}CH_2O]^+$= 217.1103, found: 217.1100.



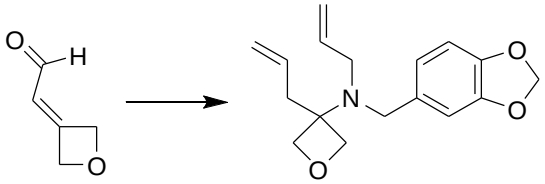
3-allyl-N-(benzo[d][1,3]dioxol-5-ylmethyl)oxetan-3-amine (200 mg, 0.81 mmol, 1.00 equiv) was dissolved in 5 mL dry THF. $Hg(O_2CCF_3)_2$ (659 mg, 1.42 mmol, 1.76 equiv) was added at room temperature. The mixture was heated to 60 °C (turning dark brown, formation of a grey precipitate), before it was cooled to 0 °C and a solution of sodium borohydride (70 mg, 1.8 mmol, 2.3 equiv; 0.5 M in 2 M aqueous NaOH) was added. The mixture was allowed to warm to room temperature and stirred for 2.5 h. To this mixture diethyl ether (30 mL) was added and the organic phase decanted off. The organic phase was dried over K_2CO_3, filtered, evaporated and the residue purified by chromatography (SiO_2, 2/1 to 1/2 cyclohexane/EtOAc). The material isolated with R_f = 0.31 (SiO_2, 2/1 Cyclohexane/EtOAc) was repurified (Al_2O_3, cyclohexane to 8/1 cyclohexane/EtOAc) to give 75 mg (38 %) pure product as a slightly yellowish oil that solidified upon storage in the fridge m_p = 39.2 °C (measured by DSC).

R_f = 0.31 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, 1H, J = 0.5Hz, 1.5 Hz), 6.77 (m, 2H), 5.94 (s, 2H), 4.89 (d, 2H, J = 6.8 Hz), 4.55 (d, 2H, J = 6.7 Hz), 3.92 (s, 2H), 2.58 (m, 2H), 2.19 (dd, 2H, J = 6.7Hz, 8.8 Hz), 1.69 (tt, 2H, J = 6.9Hz, 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.3, 133.7, 121.0, 108.6, 107.9, 100.8, 80.1, 66.4, 53.2, 51.4, 37.2, 20.9; IR (thin film) ν 2940, 2867, 2802, 1857, 1607, 1503, 1489, 1443, 1378, 1363, 1241, 1171, 1115, 1093, 1039, 978, 929, 865, 809, 774 cm^{-1}; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H,

6.93; N, 5.66. Found: C, 67.97; H, 7.11; N, 5.75; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M]^+$= 247.1203, found: 247.1204;.

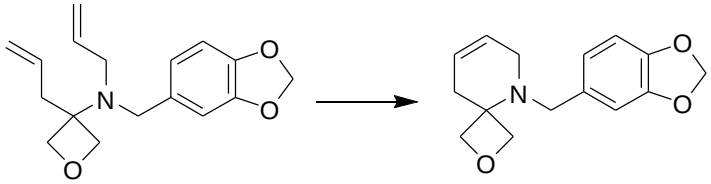


8 *5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.5]nonane* ***8***



To a solution of *N*-allyl-*N*-piperonyl amine (0.95 g, 5.0 mmol, 1.0 equiv) and DBU (7.6 µL, 50 µmol, 1.0 mol%) in 4 mL dry THF was added the a,ß-unsaturated aldehyde **24** (0.61 g, 5.0 mmol, 1.0 equiv) as a solution in 1 mL dry THF at -18 °C (MeOH/ice bath). The solution was stored for 5 d in the freezer (-18 °C), when a sample in the NMR showed 73 % conversion to the 1,4-addition product. The solution was then transferred to a solution of H_2CPPh_3 in THF(prepared by addition of *n*BuLi (2.5 M in hexanes, 5.0 mL, 13 mmol, 2.6 equiv) to a suspension of Ph_3PMeBr (4.73 g, 13.0 mmol, 2.60 equiv) in 50 mL dry THF at 0 °C). After 2 h, the reaction was quenched by adding 1 M aqueous HCl. Most of the solvents were evaporated and the aqueous phase washed 3 times with toluene. The aqueous phase was then 3 times extracted with chloroform. The combined chloroform phases were evaporated and the residue treated with aqueous Na_2CO_3 and extracted 4 times with diethyl ether. The combined diethyl ether phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 20/1 to 2/1 cyclohexane/EtOAc) to give 0.77 g (53 %) pure product as colorless oil.

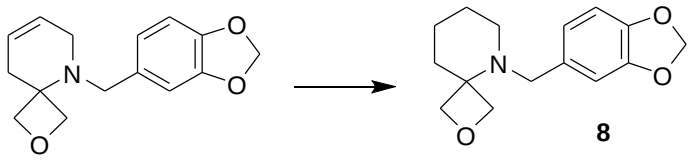
R_f = 0.60 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.76 (m, 2H), 6.09 (m, 1H), 5.94 (m, 2H), 5.72 (m, 1H), 5.24 (m, 2H), 5.04 (dddd, 2H, J = 1.0Hz, 2.5Hz, 3.0Hz, 10.1 Hz), 4.59 (d, 2H, J = 6.2 Hz), 4.26 (d, 2H, J = 6.3 Hz), 3.48 (s, 2H), 3.07 (d, 2H, J = 6.6 Hz), 2.63 (d, 2H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.4, 136, 134.0, 133.9, 121.1, 118.2, 116.7, 108.7, 107.7, 100.8, 79.8, 63.2, 53.0, 53.6, 36.2; IR (thin film) ν 3073, 2943, 2873, 1364, 1488, 1441, 1380, 1238, 1182, 1093, 1039, 981, 918, 867, 808, 779 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{21}NO_3$ $[M]^+$= 287.1516, found: 287.1518.



To a solution of *N*,3-diallyl-*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)oxetan-3-amine (760 mg, 2.64 mmol, 1.00 equiv) in 100 mL dry methylene choride was added *p*TosOH·H_2O (503 mg, 6.64 mmol, 1.00 equiv) at room temperature. The mixture was stirred until complete salvation (30 minutes) and then degassed twice (freezing with liquid nitrogen, then applying high vacuum, melting under Argon atmosphere). Grubbs II catalyst (56 mg, 66 µmol, 2.5 mol%) was added and the mixture stirred for 15 h at room temperature, before 1 M aqueous NaOH was added and the mixture stirred for 15 minutes. The aqueous phase was extracted 3 times with methylene choride. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 20/1 to 2/1 cyclohexane to EtOAc) to give 604 mg pure product (88 %) as a white solid (m_p = 76 – 77 °C).

R_f = 0.29 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.77 (m, 2H), 5.93 (m, 2H), 5.77 (m, 1H), 5.55 (m, 1H), 4.66 (d, 2H, J = 6.0 Hz), 4.30 (d, 2H, J = 6.1 Hz), 3.42 (s, 2H), 3.07 (m, 2H), 2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.4, 133.1, 125.0, 123.3, 121.5, 109.0, 107.7, 100.8, 81.1, 59.1, 52.2,

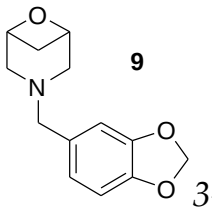
45.0, 29.8; IR (thin film) ν 3026, 2868, 1608, 1502, 1490, 1441, 1384, 1342, 1251, 1184, 1118, 1093, 1039, 980, 918, 810, 654 cm^{-1}; Anal. Calcd for $C_{15}H_{17}NO_3$; HRMS (EI) calcd for $C_{15}H_{17}NO_3$: $[M]^+$= 259.1203, found: 259.1202.



8

Through a mixture of 5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.5]non-7-ene (552 mg, 2.13 mmol, 1.00 equiv) and 5 w% Rh/C (39 mg) in 100 mL MeOH under hydrogen was bubbled hydrogen for 45 minutes, when a sample in the NMR indicated full consumption of starting material. The mixture was filtered through a plug of Celite, the filtrate evaporated and the residue purified by chromatography (SiO_2, 8/1 to 2/1 cyclohexane/EtOAc) to give 438 mg pure product (79 %) as a white solid (m_p = 44-44.5 °C)

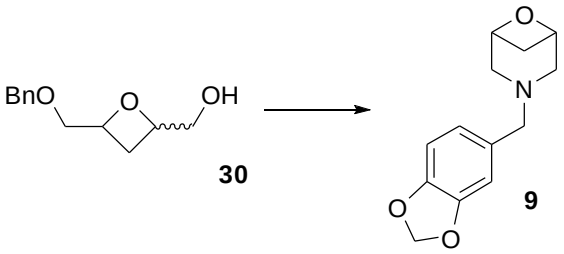
R_f = 0.37(SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, 1H, J = 1.1 Hz), 6.80 (d, 1H, J = 7.9 Hz), 6.74 (d, 1H, J = 7.9 Hz), 4.75 (d, 2H, J = 6.4 Hz), 4.36 (d, 2H, J = 6.4 Hz), 3.74 (s, 2H), 2.41 (m, 2H), 1.93 (m, 2H), 1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.2, 133.9, 121.0, 108.5, 107.7, 100.7, 79.0, 61.7, 52.7, 47.5, 33.8, 22.9, 21.3; IR (thin film) ν 2934, 2867, 1608, 1502, 1489, 1441, 1375, 1357, 1249, 1133, 1103, 1039, 979, 928, 864, 810, 775 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.94; H, 7.37; N, 5.36; HRMS (EI) calcd for $C_{15}H_{19}NO_3$: $[M\text{-}CH_3O]^+$= 230.1176, found: 230.1175.



9

3-(benzo[d][1,3]dioxol-5-ylmethyl)-6-oxa-3-azabicyclo[3.1.1]heptane

9

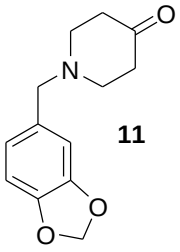


30 **9**

Cis/trans-(4-Benzyloxymethyl-oxetan-2-yl)-methanol[5] (216 mg, 1.04 mmol, 1.00 equiv) was hydrogenated at 1.2 bar for 2 h over 73 mg (0.10 eq) 20% $Pd(OH)_2/C$ in 5 ml MeOH at room temperature. The suspension was filtered and concentrated to give crude cis/trans-(4-hydroxymethyl-oxetan-2-yl)-methanol as a yellow liquid. This first intermediate was dissolved in 5 ml dry pyridine at 0 °C under argon. MsCl (0.32 ml, 4.2 mmol, 4.0 eq) was added drop wise and the mixture was stirred overnight, allowing the ice bath to expire. The mixture was poured onto cold water, acidified with 4M aq. HCl and extracted with methylene choride. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude oily mixture containing cis/trans-4-methanesulfonyloxymethyl-oxetan-2-ylmethyl methanesulfonate. This second intermediate was dissolved in 5 ml dry dioxane and piperonyl amine (0.62 ml, 5.0 mmol, 4.8 eq) was added drop wise at reflux. The mixture was further stirred for 16 h at reflux, evaporated, the mixture suspended in EtOAc and filtered (Sartorius). After concentration (625 mg) the product was chromatographed (MPLC, 80 g SiO_2, EtOAc (200 ml), EtOAc/iPrOH 99:1, 49:1, 19:1, 9:1, 4:1, 1:1 (100 ml each)) to give 48 mg 3-benzo[1,3]dioxol-5-ylmethyl-6-oxa-3-aza-bicyclo[3.1.1]heptane as a yellow liquid. Analysis by HPLC showed a purity of 97.5 %. Prior to the measurements, an additional purification via preparative HPLC on a Chiralpak AD column was conducted.

R_f = 0.30 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 5.94 (s, 2H), 4.49 (d, J = 6.3 Hz, 2H), 3.66 (s, 2H), 3.04 (d, J = 11.4 Hz, 2H), 3.05 (q, J = 7.2 Hz, 1H), 2.77 (d, J = 11.4, 2H), 2.41 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 147.7, 146.5, 132.6, 121.7109.1, 108.4, 100.9, 80.2, 60.7, 55.4, 30.5; IR (thin film) ν 2960, 2877, 2808, 1685, 1609, 1502, 1487, 1439, 1389, 1361, 1239, 1179, 1148, 1116, 1094, 1034, 958, 926, 877, 836, 806, 772, 714 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_3$: $[M+H]^+$ = 234.11247, Found: 234.11242.

Reference Compounds

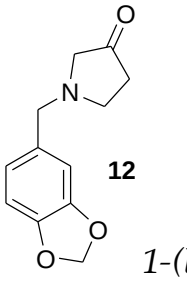


11

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-4-one[6] ***11***

4-hydroxy-piperidine (1.0 g, 10 mmol, 1.0 equiv) and piperonyl chloride (1.7 g, 10 mmol, 1.0 equiv) were dissolved in 20 mL DMF and stirred overnight at room temperature. Brine was added and diethyl ether. The aqueous phase was extracted two times with diethyl ether. The combined organic phases were washed with brine 5 times, dried over $MgSO_4$, filtered, evaporated and the residue (~95 % pure by NMR) used without further purification (R_f = 0.61 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.85 (s, 1H), 6.74 (t, *J*=3.9 Hz, 2H), 6.00 – 5.86 (m, 2H), 3.77 – 3.57 (m, 1H), 3.40 (s, 2H), 2.73 (d, *J*=11.7, 2H), 2.11 (t, *J*=10.8, 2H), 1.88 (dd, *J*=4.0 Hz, 12.8, 2H), 1.65 – 1.50 (m, 2H), 1.50 – 1.42 (m, 1H); IR (thin film) ν 3341, 2939, 2360, 1490, 1442, 1367, 1245, 1096, 1064, 4040, 933, 810, 778 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}NO_3$: $[M-H]^+$= 234.1125, found: 234.1125). From this material 0.70 g (3.0 mmol, 1.0 equiv) were dissolved in mixture 7 mL dry benzene and 3.5 mL DMSO, followed by the addition of DCC (1.9 g, 9.0 mmol, 3.0 equiv) and dry pyridine (0.24 mL, 3.0 mmol, 1.0 equiv). After cooling to 0 °C, TFA (0.11 mL, 3.0 mmol, 1.0 equiv) was added dropwise and the mixture then stirred over night, allowing it to warm to room temperature. EtOAc (50 mL) was added and the mixture filtered. The filtrate was washed with brine 3 times, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 2/1 cyclohexane/EtOAc to EtOAc) to give 0.39 g pure product as white crystalline solid (m_p = 65-69°C).

R_f = 0.14 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.90 (s, 1H), 6.77 (d, *J*=0.9 Hz, 2H), 5.96 (s, 2H), 3.53 (s, 2H), 2.73 (t, *J*=6.1 Hz, 4H), 2.45 (t, *J*=6.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 147.6, 132.0, 121.9, 109.1, 107.8, 100.9, 61.7, 52.8, 41.4; IR (thin film) ν 3323, 2911, 2808, 1716, 1623, 1502, 1489, 1442, 1368, 1342, 1244, 1195, 1113, 1085, 1038, 933, 866, 799, 776 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.84; N, 6.00. Found: C, 66.94; H, 6.48; N, 6.00; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$, 233.1047, found, 233.1046



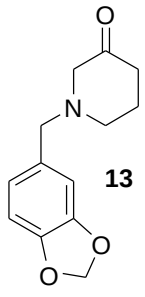
12

1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-one[7] ***12***

3-hydroxy-pyrrolidine (0.30 g, 3.5 mmol, 1.0 equiv), piperonyl chloride (0.59 g, 3.5 mmol, 1.0 equiv) and K_2CO_3 (2.9 g, 21 mmol) were disperged in 20 mL DMF and stirred overnight at room temperature. Brine was added and diethyl ether. The aqueous phase was extracted two times with diethyl ether. The combined organic phases were washed with brine 5 times, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (Al_2O_3, 8/1 to 1/1 cyclohexane/EtOAc) to give pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ol (0.67 g, 88

% yield). This material (0.67 g, 3.1 mmol, 1.0 equiv) was added at -78 °C to a solution containing DMSO (0.43 mL, 6.1 mmol, 2.0 equiv) and Oxalyl chloride (0.39 mL, 4.6 mmol, 1.5 equiv) in a way that the temperature of the mixture stays below -60 °C. Then, triethyl amine (1.3 mL, 9.2 mmol, 3.0 equiv) was added drop wise and after stirring for 2 h at -78 °C, the mixture was allowed to warm to room temperature. Aqueous 1 M NaOH was added and the aqueous phase extracted 3 times with methylene choride. The combined organic phases were washed with brine, dried over K_2CO_3, filtered, and evaporated. The residue was purified by chromatography (SiO_2, 4/1 to 2/1 cyclohexane/EtOAc) to give 0.32 g pure product (48 %) as a colorless oil that decomposes quickly when stored at room temperature.

R_f = 0.17 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.84 (s, 1H), 6.75 (d, *J*=1.0 Hz, 2H), 5.94 (s, 2H), 3.61 (s, 2H), 2.96 – 2.84 (m, 5H), 2.40 (t, *J*=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 147.6, 146.7, 131.0, 121.7, 109.0, 107.9, 100.9, 61.5, 60.5, 51.2, 38.1; IR (thin film) ν 2909, 2800, 1756, 1608, 1502, 1490, 1443, 1383, 1330, 1246, 1187, 1132, 1106, 1038, 928, 874, 810 cm^{-1}; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.60; H, 6.13; N, 6.36; HRMS (EI) calcd for $C_{12}H_{13}NO_3$ $[M]^+$, 218.0890, found, 219.0888

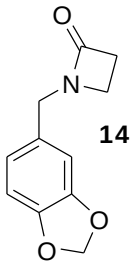


13

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-3-one ***13***

3-hydroxy-piperidine (3.0 g, 30 mmol, 1.0 equiv), piperonyl chloride (5.1 g, 30 mmol, 1.0 equiv) and K_2CO_3 (25 g, 180 mmol) were disperged in 20 mL DMF and stirred overnight at room temperature. Brine was added and diethyl ether. The aqueous phase was extracted two times with diethyl ether. The combined organic phases were washed with brine 5 times, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (Al_2O_3, 8/1 to 1/1 cyclohexane/EtOAc) to give pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-3-ol (4.4 g, 91 w% by NMR, rest DMF and EtOAc, yield 56 %) as a white solid (mp = 57-58 °C; R_f = 0.14 (SiO_2, 2/1 cyclohexane/EtOAc); IR (thin film) ν 3362, 2937, 2800, 1666, 1608, 1502, 1489, 1442, 1392, 1369, 1242, 1155, 1097, 1039, 973, 930, 885, 867, 810, 775 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}NO_3$ $[M]^+$, 234.1125, found, 234.1124). Of this material (0.50 g, 2.1 mmol, 1.0 equiv) was added at -78 °C to a solution containing DMSO (0.30 mL, 4.2 mmol, 2.0 equiv) and Oxalyl chloride (0.27 mL, 3.2 mmol, 1.5 equiv) in a way that the temperature of the mixture stays below -60 °C. Then, triethyl amine (0.88 mL, 6.4 mmol, 3.0 equiv) was added drop wise, and after stirring for 2 h at -78 °C, the mixture was allowed to warm to room temperature. Aqueous 1 M NaOH was added and the aqueous phase extracted 3 times with methylene choride. The combined organic phases were washed with brine, dried over K_2CO_3, filtered, and evaporated. The residue was purified by chromatography (SiO_2, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.21 g pure product (77 %) as a colorless crystals (mp =54-55 °C) that decompose quickly when stored at room temperature.

R_f = 0.23 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.85 – 6.78 (m, 1H), 6.78 – 6.67 (m, 2H), 5.92 (s, 2H), 3.49 (s, 2H), 2.98 (s, 2H), 2.64 (dd, *J*=4.1 Hz, 6.9, 2H), 2.36 (t, *J*=6.9 Hz, 2H), 1.94 (dt, *J*=6.9 Hz, 12.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 147.6, 146.7, 130.9, 122.1, 109.2, 107.8, 100.8, 64.3, 62.1, 51.3, 38.6, 23.8; IR (thin film) ν 2928, 2803, 1714, 1605, 1483, 1441, 1245, 1124, 1038, 987, 933, 870, 808 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.47; N, 5.93; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$, 233.1047, found, 233.1048

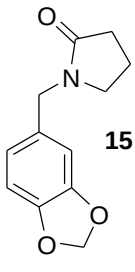


14

1-(benzo[d][1,3]dioxol-5-ylmethyl)azetidin-2-one ***14***

To a solution of piperonyl amine (1.6 mL, 13 mmol, 1.1 equiv) and triethyl amine (2.5 mL, 18 mmol, 1.5 equiv) was added 3-bromopropanoyl chloride (1.2 mL, 12 mmol, 1.0 equiv). The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase extracted 3 times with EtOAc. The combined organic phases were washed 3 times with brine, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 20/1 to 1/2 cyclohexane/EtOAc) to give 2.4 g pure N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-bromopropanamide (R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.82 – 6.76 (m, 1H), 6.74 (t, *J*=1.0 Hz, 2H), 5.94 (s, 2H), 4.39 (dd, *J*=5.7 Hz, 13.7 Hz, 2H), 3.66 (t, *J*=6.6 Hz, 2H), 2.77 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) d = 169.4, 147.8, 147.0, 131.5, 121.1, 108.3, 108.2, 101.0, 43.5, 39.7, 27.4; IR (thin film) ν 3267, 3075, 2899, 1634, 1556, 1503, 1445, 1420, 1366, 1261, 1223, 1190, 1100, 1037, 926, 872, 812 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9NO_3Br$ $[M]^+$ = 284.9995, found, 284.9998). Of this material 1.0 g (3.5 mmol, 1.0 equiv) were dissolved in 45 mL dry methylene choride. This solution was added over 6 h to a suspension of finely powdered KOH (0.23 g, 4.2 mmol, 1.2 equiv) in 45 mL methylene choride. After filtration and evaporation of the filtrate, the residue was purified by chromatography (SiO_2, 4/1 cyclohexane/EtOAc to EtOAc) to give 0.22 g (31 %) pure product as a colorless oil.

R_f = 0.39 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.80 – 6.62 (m, 3H), 5.94 (s, 2H), 4.26 (s, 2H), 3.12 (t, *J*=4.1 Hz, 2H), 2.92 (t, *J*=4.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.9, 147.0, 129.4, 121.5, 108.5, 108.3, 101.1, 46.0, 38.5, 36.9; IR (thin film) ν 3477, 2962, 2904, 1744, 1608, 1503, 1491, 1446, 1404, 1371, 1296, 1247, 1190, 1124, 1098, 1037, 926, 865, 811, 770, 739, 713 cm^{-1}; Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.09; H, 5.41; N, 6.79; HRMS (EI) calcd for $C_{11}H_{11}NO_3$ $[M]^+$, 205.0733, found, 205.0733



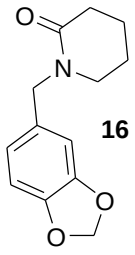
15

1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-2-one ***15***

To a solution of ?-butyro lactam (3.5 mL, 45 mmol, 1.0 equiv) in 50 mL dry THF was cautiously added sodium hydride (60 % in mineral oil, 2.0 g, 50 mmol, 1.1 equiv) at 0 °C. After stirring for 30 minutes, a solution of piperonyl bromide[8] (9.7 g, 45 mmol, 1.0 equiv) in 10 mL dry THF was slowly added over 10 minutes, the mixture allowed to warm to rt and stirred over night. Brine and water were added and the mixture was extracted 3 times with EtOAc. The combined organic phases were washed once with brine, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 2/1 cyclohexane/EtOAc to EtOAc) to give 5.67 g pure product (58 %) as white crystals (m_p = 63-65 °C).

R_f = 0.11 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.79 – 6.65 (m, 3H), 5.93 (s, 2H), 4.34 (s, 2H), 3.30 – 3.17 (m, 2H), 2.42 (t, *J*=8.1 Hz, 2H), 1.97 (dq, *J*=7.5 Hz, 11.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) d

= 174.6, 147.8, 146.9, 130.4, 121.4, 108.5, 108.1, 101.0, 46.5, 46.4, 31.1, 17.8; IR (thin film) ν 2895, 1682, 1491, 1443, 1245, 1037, 925, 810, 772 cm^{-1}; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 5.97; N, 6.27; HRMS (EI) calcd for $C_{12}H_{13}NO_3$: $[M]^+$= 219.0890, found: 219.0891.

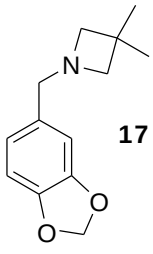


16

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-2-one ***16***

To a solution of δ-valero lactam (4.5 g, 45 mmol, 1.0 equiv) in 50 mL dry THF was cautiously added sodium hydride (60 w% in mineral oil, 2.0 g, 50 mmol, 1.1 equiv) at 0 °C. After stirring for 30 minutes, a solution of piperonyl bromide[8] (9.7 g, 45 mmol, 1.0 equiv) in 10 mL dry THF was slowly added over 10 minutes, the mixture allowed to warm to room temperature and stirred over night. Brine and water were added and the mixture was extracted 3 times with EtOAc. The combined organic phases were washed once with brine, dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, 4/1 cyclohexane/EtOAc to EtOAc) to give 7.78 g pure product (58 %) as white crystals (m_p = 68-69 °C).

R_f = 0.09 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.81 – 6.64 (m, 3H), 5.94 (s, 2H), 4.49 (s, 2H), 3.19 (d, *J*=6.0 Hz, 2H), 2.44 (d, *J*=6.3 Hz, 2H), 2.17 (s, 3H), 1.85 – 1.65 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) d = 169.6, 147.8, 146.7, 131.1, 121.4, 108.5, 108.0, 100.9, 49.9, 47.1, 32.5, 23.3, 21.5; IR (thin film) ν 2945, 1638, 1491, 1443, 1352, 1241, 1177, 1038, 927, 808, 772, 664 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.03; H, 6.49; N, 5.95; HRMS (EI) calcd for $C_{13}H_{15}NO$: $[M]^+$= 233.1046, found: 233.1045.

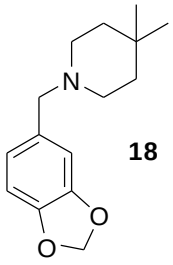


17

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylazetidine ***17***

To a solution of 3-chloro-2,2-dimethylpropanal[9] (3.5 g, 29 mmol, 1.0 equiv) in 30 mL dry diethyl ether was added $MgSO_4$?0.5 H_2O (3.0 g), followed by piperonyl amine (3.7 mL, 30 mmol, 1.0 equiv). After stirring for 4 h, a sample in the NMR indicated full conversion. The mixture was filtered, the filtrate slowly added to a solution of $LiAlH_4$ (6.0 mL of 4.0 M solution in diethyl ether, 30 mmol, 1.0 equiv) at rt. The mixture was then refluxed over night, cooled to room temperature, before Na_2SO_4?10H_2O was slowly added. After stirring for 20 minutes, the solvent was decanted off and the residue refluxed with 5x20 mL EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue filtered through a column (Al_2O_3, 4/1 cyclohexane/EtOAc) to give 3.8 g pure product (58 %) as a colorless oil.

R_f = 0.74 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.80 (d, *J*=0.5 Hz, 1H), 6.77 – 6.67 (m, 2H), 5.92 (s, 2H), 3.50 (s, 2H), 2.95 (s, 4H), 1.21 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.4, 146.2, 132.6, 121.2, 108.7, 107.8, 100.7, 66.5, 63.4, 31.4, 27.4; IR (thin film) ν 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1041, 937, 810, 776 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.07; H, 8.00; N, 6.392951, 2902, 2814, 1609, 1503, 1489, 1442, 1374, 1337, 1247, 1187,1159, 1115, 1094, 1041, 939, 886, 863, 811, 759; HRMS (EI) calcd for $C_{13}H_{17}NO_2$: $[M]^+$= 219.1254, found: 219.1252.

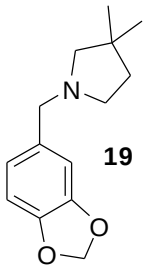


18

*1-(benzo[d][1,3]dioxol-5-ylmethyl)-4,4-dimethylpiperidine **18***

To a solution of 4,4-dimethylpiperidine-2,6-dione (5.7 g, 40 mmol, 1.0 equiv) in 45 mL DMF was added KOH (2.5 g, 44 mmol, 1.1 equiv) at 0 °C. After stirring for 30 minutes, piperonyl bromide[8] (9.1 g, 42 mmol, 1.1 equiv) was added as a solution in 8 mL DMF. The mixture was then stirred at room temperature for 5 h and then poured on water. The aqueous phase was extracted 3 times with diethyl ether and the combined organic phases were washed with 2 M aqueous NaOH twice, once with water and once with saturated aqueous NH_4Cl. After drying over $MgSO_4$, filtration and evaporation, the residue was purified by chromatography (SiO_2, 8/1 to 2/1 cyclohexane/EtOAc) to 3.9 g pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)-4,4-dimethylpiperidine-2,6-dione (R_f = 0.33 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.88 (d, *J*=7.4 Hz, 2H), 6.71 (d, *J*=8.6 Hz, 1H), 5.91 (s, 2H), 4.85 (s, 2H), 2.51 (s, 4H), 1.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 147.3, 146.7, 131.0, 122.6, 109.6, 108.0, 100.9, 46.5, 42.5, 29.3, 27.8; IR (thin film) ν 2959, 2896, 2779, 1724, 1674, 1609, 1504, 1491, 1446, 1365, 1344, 1330, 1249, 1137, 1101, 1038, 926, 891 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{23}NO_2$ $[M]^+$, 275.1157, found, 275.1157) as a white solid (mp = 70-72 °C). Of this material, 2.8 g (10 mmol, 1.0 equiv) were dissolved in 100 mL dry diethyl ether and slowly added to a solution of $LiAlH_4$ (1.2 g, 30 mmol, 3.0 equiv) in 100 mL dry diethyl ether at 0 °C. The mixture was then allowed to warm to room temperature refluxed for 12 h and cooled to 0 °C. Na_2SO_4?10H_2O was slowly added, the mixture stirred for 20 minutes at room temperature and filtered. The filter cake was boiled with 2 portions EtOAc for 30 seconds. The combined filtrates were dried over Na_2SO_4, filtered, evaporated and the residue purified by Kugelrohr distillation to give 1.8 g pure product as white crystals (mp = 53-54°C).

^{1}H NMR (300 MHz, $CDCl_3$) d = 6.85 (s, 1H), 6.74 (s, 2H), 5.92 (s, 2H), 3.41 (s, 2H), 2.44 – 2.23 (m, 4H), 1.44 – 1.29 (m, 4H), 0.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.3, 132.6, 122.1, 109.5, 107.7, 100.7, 63.3, 50.0, 38.8, 28.6; IR (thin film) ν 2948, 2910, 2838, 2805, 2765, 1609, 1502, 1489, 1442, 1369, 1331, 1295, 1241, 1207, 1182, 1128, 1105, 1042, 989, 940, 865, 810, 799, 776, 715 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.68; H, 8.46; N, 5.55; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1567, found, 247.1565



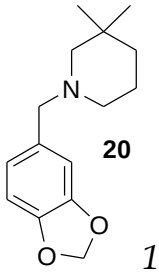
19

*1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpyrrolidine **19***

A solution of 3,3-dimethyldihydrofuran-2,5-dione (1.0 g, 7.8 mmol, 1.0 equiv) and piperonyl amine (1.0 mL, 7.8 mmol, 1.0 equiv) in 30 mL dry Toluene were refluxed overnight using a Dean-Stark trap. After cooling to room temperature, aqueous HCl (1 M) was added and the aqueous phase extracted 3 times with EtOAc. The organic phases were washed with brine, filtered, evaporated and the crude 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpyrrolidine-2,5-dione (R_f = 0.33 (SiO_2, 2/1 cyclohexane/EtOAc) used without further purification. This material was dissolved in 90 mL dry diethyl ether and slowly added at 0 °C to a solution of $LiAlH_4$ (0.89 g, 2.3 mmol, 3.0 equiv) in 45 mL dry diethyl ether. The mixture was then allowed to warm to room temperature refluxed

for 12 h and cooled to 0 °C. Na_2SO_4?$10H_2O$ was slowly added, the mixture stirred for 20 minutes at room temperature and filtered. The filter cake was boiled with 2 portions EtOAc for 30 seconds. The combined filtrates were dried over Na_2SO_4, filtered, evaporated and the residue purified by Kugelrohr distillation to give 1.3 g pure product as waxy solid (mp = 33-35°C).

^{1}H NMR (300 MHz, $CDCl_3$) d = 6.87 (s, 1H), 6.80 – 6.67 (m, 2H), 5.93 (s, 2H), 3.49 (s, 2H), 2.59 (t, *J*=7.0 Hz, 2H), 2.27 (s, 2H), 1.58 (t, *J*=7.0 Hz, 2H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.1, 133.7, 121.4, 109.1, 107.7, 100.7, 68.2, 60.4, 54.3, 39.9, 37.7, 29.7; IR (thin film) ν 2952, 2868, 2783, 1609, 1503, 1489, 1442, 1378, 1346, 1316, 1245, 1185, 1106, 1041, 940, 864, 810, 776 cm^{-1}; Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.78; H, 8.05; N, 6.11; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ $[M]^+$, 233.1411, found, 233.1408

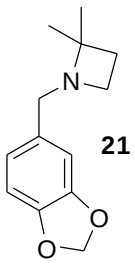


20

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine ***20***

To a solution of 3,3-dimethyldihydro-2H-pyran-2,6(3H)-dione (2.8 g, 20 mmol, 1.0 equiv) in 40 mL THF was added piperonyl amine (3.3 g, 22 mmol, 1.1 equiv) at room temperature. The mixture was stirred for 30 minutes, before the solvent was evaporated. The residue was dissolved in EtOAc and 1 M aqueous HCl was added and the aqueous phase extracted 3 times with EtOAc. The organic phase was washed once with brine, dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in 20 mL acetic anhydride and 3.5 mL triethyl amine was added. The mixture was heated to 80 °C and stirred for 1 h. Then the solvent was evaporated. The residue was dissolved in EtOAc and 1 M aqueous HCl was added and the aqueous phase extracted 3 times with EtOAc. The organic phase was washed once with 1 M aqueous HCl, brine and saturated aqueous sodium bicarbonate, dried over $MgSO_4$, filtered, evaporated and the residue purified via chromatography (SiO_2, 1/1 cyclohexane/EtOAc) to give 2.7 g 90 w% (NMR) pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine-2,6-dione (49 %) (^{1}H NMR (300 MHz, $CDCl_3$) d = 6.82 (dd, *J*=1.7 Hz, 6.0, 2H), 6.69 (d, *J*=8.4 Hz, 1H), 5.90 (s, 2H), 4.82 (s, 2H), 2.71 (t, *J*=6.8 Hz, 2H), 1.78 (t, *J*=6.8 Hz, 2H), 1.25 (s, 6H); IR (thin film) ν 2969, 1805, 1765, 1722, 1674, 1504, 1491, 1446, 1690, 1355, 1325, 1282, 1247, 1164, 1038, 1017, 927, 885, 808, 778 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_4$ $[M]^+$, 275.1153, found, 275.1155). To a solution of 0.29 g $LiAlH_4$ (7.7 mmol, 3.0 equiv) in 15 mL dry diethyl ether was added a solution 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine-2,6-dione in 30 mL dry diethyl ether slowly at 0 °C. The mixture was then allowed to warm to room temperature and refluxed for 2.5 h. After cooling to room temperature, Na_2SO_4?$10H_2O$ was slowly added, stirred for 20 minutes and filtered. The filter cake was refluxed once with EtOAc, the combined filtrates evaporated and the residue purified by chromatography (SiO_2, 20/1 to 4/1 cyclohexane/EtOAc) to give 0.26 g pure product as a slightly yellowish oil (42 %).

R_f = 0.50 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.88 (s, 1H), 6.74 (d, *J*=0.8 Hz, 2H), 5.94 (s, 2H), 3.33 (s, 2H), 2.29 (s, 2H), 1.98 (s, 2H), 1.58 (dt, *J*=5.6 Hz, 11.1 Hz, 2H), 1.26 – 1.14 (m, 2H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.1, 133.4, 121.4, 108.9, 107.5, 100.6, 65.7, 62.9, 54.4, 37.5, 30.8, 27.2, 22.6; IR (thin film) ν 2974, 2771, 1608, 1488, 1441, 1365, 1240, 1181, 1107, 1042, 991, 936, 865, 804, 774 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.97; H, 8.46; N, 5.79; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1567, found, 247.1567

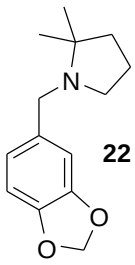


21

1-(benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethylazetidine ***21***

A mixture of ethyl 3-methylbut-2-enoate (4.1 mL, 30 mmol, 1.0 equiv) and piperonyl amine was stirred at 120 °C for 6 d in a sealed vessel. The mixture was then separated by chromatography (SiO_2, methylene choride to 6 % MeOH in methylene choride) to give 1.9 g pure ethyl 3-(benzo[d][1,3]dioxol-5-ylmethylamino)-3-methylbutanoate in 23 % yield (R_f = 0.19 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.91 – 6.84 (m, 1H), 6.84 – 6.69 (m, 2H), 5.95 – 5.87 (m, 2H), 4.14 (q, *J*=7.1 Hz, 2H), 3.62 (s, 2H), 2.49 (s, 2H), 1.71 (s, 1H), 1.26 (t, *J*=7.1 Hz, 3H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) d = 171.8, 147.5, 146.2, 134.9, 121.1, 108.9, 108.0, 100.7, 60.0, 52.4, 46.6, 44.1, 27.5, 14.2; IR (thin film) ν 3410, 2972, 2901, 1726, 1490, 1442, 1368, 1327, 1249, 1098, 1039, 931, 809 cm^{-1} ; HRMS (EI) calcd for $C_{15}H_{21}NO_4$: $[M-H]^+$= 278.1387, found: 278.1388.). This material (1.9 g, 6.7 mmol, 1.0 equiv) was added slowly as a solution in 10 mL dry diethyl ether to a solution of $LiAlH_4$ (5.0 mL of a 4.0 M solution in diethyl ether, 20 mmol, 3.0 equiv) in 40 mL dry diethyl ether at room temperature. After stirring overnight at room temperature, Na_2SO_4?10H_2O was slowly added. After stirring for 20 minutes, the mixture was filtered, the filter cake cooked with 5x20 mL EtOAc for 30 seconds each. The combined filtrates were dried over Na_2SO_4, filtered, evaporated and the residue (2.5 g pure amino alcohol, R_f = 0.27 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.78 (s, 1H), 6.74 (d, *J*=0.6 Hz, 2H), 5.95 – 5.88 (m, 2H), 3.92 – 3.81 (m, 2H), 3.66 (s, 2H), 1.68 – 1.57 (m, 2H), 1.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.6, 146.6, 133.7, 121.2, 108.8, 108.1, 100.8, 60.5, 54.2, 46.3, 40.1, 26.8; IR (thin film) ν 3298, 2965, 1609, 1490, 1442, 1367, 1249, 1039, 928, 809 cm^{-1} ; HRMS (EI) calcd for $C_{13}H_{19}NO_3$: $[M-CH_3]^+$= 222.1125, found: 222.1124.) dissolved without further purification in 100 mL dry acetonitrile. Triphenyl phosphine (4.1 g, 16 mmol, 2.3 equiv) was added, followed under cooling (ice bath) by carbontetrabromide (5.2 g, 16 mmol, 2.3 mmol) and triethyl amine (2.9 mL, 21 mmol, 3.1 equiv). After stirring overnight, the NMR showed full conversion. The mixture was evaporated and the residue dispersed in diethyl ether. Aqueous 1 M NaOH (60 mL) was added and the aqueous layer extracted 3 times with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, methylene choride to 10 % MeOH in methylene choride) to give 656 mg pure product (44 %) as a slightly yellowish oil.

R_f = 0.11 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.88 – 6.80 (m, 1H), 6.77 – 6.63 (m, 2H), 5.91 (s, 2H), 3.44 (s, 2H), 3.15 – 3.01 (m, 2H), 1.94 – 1.77 (m, 2H), 1.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.3, 146.6, 133.1, 121.4, 109.2, 107.8, 100.7, 63.4, 55.0, 49.3, 31.9, 25.0; IR (thin film) ν 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1041, 937, 810, 776 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.04; H, 7.80; N, 6.58; HRMS (EI) calcd for $C_{13}H_{17}NO_2$: $[M]^+$= 219.1254, found: 219.1253.



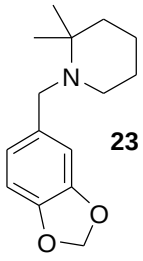
22

1-(benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethylpyrrolidine ***22***

To a solution of 1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-2-one (**15**) (2.2 g, 10 mmol, 1.0 equiv) in 20 dry THF was added $ZrCl_4$ (2.3 g, 10 mmol, 1.0 equiv) in 2 portions at -10 °C. After stirring for 30 minutes, a solution of

MeMgBr (3.0 M in diethyl ether, 20 mL, 60 mmol, 6.0 equiv) was added slowly enough not to exceed a temperature of the reaction mixture of 0 °C. The mixture was stirred for 4 h and allowed to warm to room temperature. Aqueous NaOH (30 w%) was added slowly and the aqueous phase extracted 3 times with methylene choride. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (Al_2O_3, 20/1 cyclohexane/EtOAc) to give 0.84 g pure product (36 % yield) as a yellowish solid (mp = 33-34 °C).

R_f = 0.91 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.86 (dd, *J*=0.5 Hz, 1.4, 1H), 6.78 – 6.68 (m, 2H), 5.92 (s, 2H), 3.42 (s, 2H), 2.60 (ddd, *J*=2.7 Hz, 5.4, 6.0, 2H), 1.68 (d, *J*=2.9 Hz, 4H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 121.2, 109.0, 107.7, 100.7, 60.0, 53.0, 50.9, 40.0, 23.1, 20.5; IR (thin film) 2960, 2795, 1609, 1489, 1441, 1381, 1360, 1242, 1180, 1094, 1041, 940, 865, 809, 776 cm^{-1}; Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.13; N, 5.96; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ $[M]^+$, 233.1410, found, 233.1411

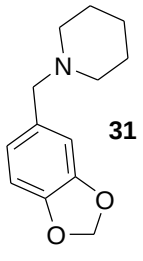


23

1-(benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethylpiperidine ***23***

To a solution of 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-2-one (**16**) (2.3 g, 10 mmol, 1.0 equiv) in 20 dry THF was added $ZrCl_4$ (2.3 g, 10 mmol, 1.0 equiv) in 2 portions at -10 °C. After stirring for 30 minutes, a solution of MeMgBr (3.0 M in diethyl ether, 20 mL, 60 mmol, 6.0 equiv) was added slowly enough not to exceed a temperature of the reaction mixture of 0 °C. The mixture was stirred for 4 h and allowed to warm to room temperature. Aqueous NaOH (30 w%) was added slowly and the aqueous phase extracted 3 times with methylene choride. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (Al_2O_3, cyclohexane to 4/1 cyclohexane/EtOAc) to give 0.23 g pure product (10 % yield) as a yellowish liquid.

R_f = 0.80 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.92 (dd, *J*=0.5 Hz, 1.5 Hz, 1H), 6.75 (dd, *J*=4.3 Hz, 5.1 Hz, 1H), 6.72 (dd, *J*=0.5 Hz, 7.9 Hz, 1H), 5.92 (s, 2H), 3.39 (s, 2H), 2.38 – 2.22 (m, 2H), 1.47 (s, 6H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 145.9, 135.6, 121.1, 108.8, 107.6, 100.7, 53.8, 53.3, 47.0, 40.7, 26.8, 21.4; IR (thin film) ν 2966, 2929, 2794, 1609, 1502, 1489, 1440, 1396, 1284, 1244, 1201, 1184, 1144, 1127, 1093, 1041, 940, 861, 810, 774 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.61; N, 5.76; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1568, found, 247.1567



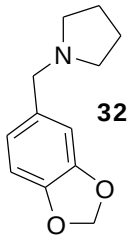
31

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidine[10] ***31***

Piperidine (0.99 mL, 10 mmol, 1.0 equiv) and piperonyl chloride (1.7 g, 10 mmol, 1.0 equiv) were dissolved in 20 mL DMF and stirred overnight at room temperature. Brine was added and diethyl ether. The aqueous phase was extracted two times with diethyl ether. The combined organic phases were washed with brine 5 times, dried over

$MgSO_4$, filtered, evaporated and the residue distilled (Kugelrohr) to give 1.64 g pure product as a colorless oil (75 %).

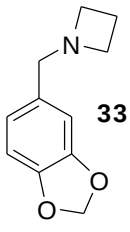
R_f = 0.84 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.88 – 6.82 (m, 1H), 6.73 (d, *J*=1.0 Hz, 2H), 5.93 (s, 2H), 3.37 (s, 2H), 2.35 (s, 4H), 1.63 – 1.49 (m, 4H), 1.49 – 1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.4, 146.2, 132.5, 122.1, 109.5, 107.7, 100.8, 63.6, 54.4, 26.1, 24.5; IR (thin film) ν 2934, 2853, 2800, 2760, 1700, 1609, 1503, 1489, 1442, 1394, 1370, 1240, 1104, 1039, 995, 933, 868, 808, 780 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 7.84; N, 6.47; HRMS (EI) calcd for $C_{13}H_{17}NO_2$: $[M]^+$= 219.1254, found: 219.1254.



1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidine ***32***

To a solution of pyrrolidine (0.80 mL, 10 mmol, 1.0 equiv) and piperonal (1.5 g, 10 mmol, 1.0 equiv) in 20 mL dry methylene choride was added $NaBH(OAc)_3$ (5.3 g, 25 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K_2CO_3 was added until complete solvation of borate byproducts. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue distilled (Kugelrohr) to give 1.50 g pure product (73 %) as a colorless oil.

Rf = 0.63 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d = 6.85 (dd, *J*=0.5 Hz, 1.4 Hz, 1H), 6.80 – 6.69 (m, 2H), 5.93 (s, 2H), 3.51 (s, 2H), 2.55 – 2.38 (m, 4H), 1.78 (dd, *J*=3.4 Hz, 7.0, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.4, 146.2, 133.3, 121.8, 109.3, 107.8, 100.8, 60.5, 54.1, 23.5; IR (thin film) ν 22964, 2784, 1502, 1489, 1441, 1247, 1040, 937, 810 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.45; N, 6.82; HRMS (EI) calcd for $C_{12}H_{15}NO_2$: $[M-H]^+$= 204.1019, found: 204.1018.



1-(benzo[d][1,3]dioxol-5-ylmethyl)azetidine ***33***

To a solution of azetidine (0.52 mL, 7.7 mmol, 1.1 equiv) and piperonal (1.1 g, 7 mmol, 1.0 equiv) in 30 mL methylene choride was added $NaBH(OAc)_3$ (3.7 g, 18 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K_2CO_3 was added until complete solvation of borate byproducts. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue purified by chromatography (SiO_2, EtOAc to 10% MeOH in CH_2Cl_2) to give 1.06 g pure product (79 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) d = 6.76 (dd, *J*=0.4 Hz, 1.0 Hz, 1H), 6.74 – 6.65 (m, 2H), 5.89 (d, *J*=0.4 Hz, 2H), 3.44 (s, 2H), 3.16 (t, *J*=7.0 Hz, 4H), 2.05 (p, *J*=7.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3) d = 147.4, 146.3, 132.1, 121.4, 108.9, 107.9, 100.7, 63.6, 54.9, 17.7; IR (thin film) ν 2958, 2820, 1503, 1499, 1375, 1301, 1249, 1176, 1114, 1040,

938, 864, 811, 773 cm^{-1}; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.80; H, 6.76; N, 7.25; HRMS (EI) calcd for $C_{11}H_{13}NO_2$: $[M]^+$= 191.0946, found: 191.0941.

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